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SUBJECT: FDA PROPOSAL TO WITHDRAW APPROVAL FOR USE OF
ANTIMICROBIAL FLOUROQUINOLONE IN POULTRY

¶1. SUMMARY: ON OCTOBER 26, 2000, THE FOOD AND DRUG ADMINISTRATION'S CENTER FOR VETERINARY MEDICINE PROPOSED WITHDRAWING ITS PREVIOUS APPROVAL FOR FLUOROQUINOLONES USED THERAPEUTICALLY IN POULTRY. THE FOLLOWING IS PROVIDED TO ASSIST POSTS IN RESPONDING TO INQUIRIES FROM LOCAL GOVERNMENT OFFICIALS AND PRESS. AS NEEDED, POSTS MAY DRAW ON TALKING POINTS PROVIDED IN PARA 12. THIS IS NOT AN ACTION REQUEST. FDA'S PROPOSAL AND RISK ASSESSMENT ARE AVAILABLE ON THE INTERNET, AS INDICATED BELOW. IF HOST GOVERNMENT CONTACTS ARE INTERESTED IN ADDITIONAL INFORMATION, THE FDA CONTACT PERSON IS: LINDA TOLLEFSON, FDA/CVM, (301) 827-6647 OR LTOLLEFS@CVM.FDA.GOV. END SUMMARY.

BACKGROUND

¶2. THE FLUORQUINOLONE ANTIMICROBIAL DRUGS ARE USED IN FOOD-PRODUCING ANIMALS TO TREAT, PREVENT AND CONTROL DISEASE. IN THE UNITED STATES, REGULATORY TERMINOLOGY NAMES THESE PRODUCTS "NEW ANIMAL DRUGS." (NOTE: WHILE USED DIFFERENTLY BY SCIENTISTS, ANTIBIOTIC AND ANTIMICROBIAL ARE USED INTERCHANGEABLY IN THIS DOCUMENT AND MEAN A PRODUCT THAT HAS THE ABILITY TO INHIBIT BACTERIA.) BEFORE ANY NEW ANIMAL DRUG CAN BE APPROVED IN THE UNITED STATES, THE DRUG'S SPONSOR MUST DEMONSTRATE THAT THE PRODUCT IS SAFE AND EFFECTIVE FOR ITS INTENDED USE. IF THE ANTIMICROBIAL DRUG IS INTENDED FOR USE IN FOOD PRODUCING ANIMALS, THE DRUG SPONSOR MUST DEMONSTRATE SAFETY FOR CONSUMERS OF
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EDIBLE ANIMAL PRODUCTS, AS WELL AS SAFETY FOR USE IN THE ANIMAL.

¶3. THE FOOD AND DRUG ADMINISTRATION (FDA) FIRST CALLED FOR SEVERAL RESTRICTIONS ON ANTIMICROBIAL USE IN FEED IN 1977. IN RECENT YEARS, CONCERNS ABOUT THE USE OF ANTIMICROBIAL PRODUCTS IN FOOD-PRODUCING ANIMALS HAVE FOCUSED ON HUMAN FOOD SAFETY, BECAUSE FOODS OF ANIMAL ORIGIN ARE IDENTIFIED AS VEHICLES OF FOODBORNE DISEASE IN HUMANS.

¶4. SINCE 1988, FDA'S CENTER FOR VETERINARY MEDICINE (CVM) HAS APPROVED NEW THERAPEUTIC ANTIMICROBIALS AS PRESCRIPTION-ONLY PRODUCTS FOR USE IN FOOD-PRODUCING ANIMALS. THIS PRESCRIPTION-ONLY POLICY IS BASED ON THE NEED TO ASSURE THE PROPER USE OF ANTIMICROBIALS THROUGH PRECISE DIAGNOSIS AND CORRECT TREATMENT OF DISEASE TO MINIMIZE ANIMAL SUFFERING AND TO AVOID DRUG RESIDUES IN FOOD. ANTIMICROBIAL PRODUCTS FOR USE IN ANIMALS MUST MEET FDA'S STANDARDS FOR SAFETY, EFFICACY, AND QUALITY TO BE APPROVED IN THE UNITED STATES.

¶5. IN THE 1990S, SEVERAL SCIENTISTS RAISED CONCERNS ABOUT THE THERAPEUTIC USE OF FLUOROQUINOLONE ANTIBIOTICS IN FOOD-PRODUCING ANIMALS. THE SCIENTISTS SAID THE USE COULD LEAD TO ENTERIC DISEASE IN HUMANS ASSOCIATED WITH FLUOROQUINOLONE-RESISTANT FOODBORNE PATHOGENS. ADDING TO THAT CONCERN WERE REPORTS OF A TEMPORAL ASSOCIATION BETWEEN THE APPROVAL OF FLUOROQUINOLONES FOR THERAPEUTIC USE IN POULTRY IN EUROPE AND THE EMERGENCE OF A FLUOROQUINOLONE-RESISTANT CAMPYLOBACTER FROM HUMANS.

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¶6. FLUOROQUINOLONES ARE CONSIDERED TO BE ONE OF THE MOST VALUABLE ANTIMICROBIAL DRUG CLASSES AVAILABLE TO TREAT HUMAN INFECTIONS BECAUSE OF THEIR SPECTRUM OF ACTIVITY, SAFETY, AND EASE OF ADMINISTRATION. THIS CLASS OF DRUGS IS EFFECTIVE AGAINST A WIDE RANGE OF HUMAN DISEASES AND IS USED BOTH IN TREATMENT AND PROPHYLAXIS OF BACTERIAL INFECTIONS IN THE COMMUNITY AND IN HOSPITALS. FLUOROQUINOLONES ARE USED ROUTINELY BY PHYSICIANS FOR THE TREATMENT OF FOODBORNE DISEASE. THESE DISEASES HAVE A MAJOR PUBLIC HEALTH CONSEQUENCE IN THE UNITED STATES.

¶7. TO FURTHER INVESTIGATE THE PUBLIC HEALTH CONCERNS REGARDING THE POTENTIAL IMPACT OF FLUOROQUINOLONE USE IN FOOD-PRODUCING ANIMALS, AND TO DETERMINE WHETHER THE 1987 FDA REPORT (WHICH CONCLUDED THAT THERAPEUTIC ANTIMICROBIALS USED FOR SHORT DURATION WERE SAFE) WAS STILL VALID, FDA HELD A JOINT ADVISORY COMMITTEE MEETING IN 1994 THAT INCLUDED THE CVM VETERINARY MEDICINE ADVISORY COMMITTEE (VMAC) AND THE CENTER FOR DRUG EVALUATION AND RESEARCH'S ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE. THE JOINT COMMITTEE RECOMMENDED THAT FLUOROQUINOLONES FOR POULTRY BE APPROVED, BUT THAT USE OF THE DRUGS SHOULD BE LIMITED TO PRESCRIPTION ONLY, THAT NO EXTRA-LABEL USE SHOULD BE ALLOWED, AND THAT RESISTANCE SHOULD BE MONITORED AFTER THE PRODUCT WAS APPROVED. APPROVAL OF BAYTRIL (TRADE NAME OF ONE PRODUCT) WAS LIMITED TO THERAPEUTIC USE, PRESCRIPTION ONLY, AND NO EXTRA-LABEL USE WAS ALLOWED.

¶8. FDA'S CVM CREATED A FLUOROQUINOLONE WORKING GROUP TO ADDRESS THE POINTS RAISED BY THE JOINT COMMITTEE. THE WORKING GROUP OFFERED SEVEN RECOMMENDATIONS, ALL OF WHICH

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WERE ACCEPTED BY CVM, AND SUBSEQUENTLY THE USE OF FLUOROQUINOLONES WAS APPROVED FOR POULTRY IN 1995 AND 1996. AS SUGGESTED IN THE RECOMMENDATIONS, THE SPONSORS AGREED TO PROVIDE BASELINE SUSCEPTIBILITY INFORMATION AND TO CONDUCT CONTINUING MONITORING OF TARGET ANIMAL PATHOGENS THROUGH THE POST-APPROVAL MONITORING PROGRAM. HOWEVER, RESISTANCE DEVELOPED TO THE FLUOROQUINOLONES IN CAMPYLOBACTER, A MAJOR FOODBORNE PATHOGEN IN HUMANS. IN NOVEMBER 1998, THE FDA ANNOUNCED DRAFT GUIDANCE FOR INDUSTRY ON THIS SUBJECT. FINALIZED IN DECEMBER 1999, THIS STATED THAT THE FDA BELIEVES IT IS NECESSARY TO CONSIDER THE POTENTIAL HUMAN HEALTH IMPACT, WHEN APPROVING SUCH DRUGS, OF THE MICROBIAL

EFFECTS ASSOCIATED WITH ANTINICROBIAL "NEW ANIMAL DRUGS" INTENDED FOR USE IN FOOD-PRODUCING ANIMALS.

¶9. THE CENTER'S CONCLUSIONS ARE BASED ON DATA FROM THE NATIONAL ANTIMICROBIAL RESISTANCE MONITORING SYSTEM (A NATIONAL SURVEILLANCE PROGRAM OPERATED BY THE CENTER IN COOPERATION WITH THE CENTERS FOR DISEASE CONTROL AND PREVENTION AND THE U.S. DEPARTMENT OF AGRICULTURE), PUBLISHED LITERATURE, AND OTHER SOURCES. THE DATA INDICATE THAT THE USE OF FLUOROQUINOLONES IN POULTRY IS A SIGNIFICANT CAUSE OF FLUOROQUINOLONE-RESISTANT CAMPYLOBACTER ON POULTRY CARCASSES, AND THEREFORE A SIGNIFICANT CAUSE OF FLUOROQUINOLONE-RESISTANT CAMPYLOBACTER INFECTIONS IN HUMANS.

¶10. ON OCTOBER 26, 2000, THE CVM ISSUED A "NOTICE OF OPPORTUNITY" FOR A HEARING ON A PROPOSAL TO WITHDRAW THE APPROVAL FOR USE OF ONE FLUOROQUINOLONE ANTIMICROBIAL IN POULTRY. THE OFFICE OF THE FEDERAL REGISTER PUBLISHED THE

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NOTICE ON OCTOBER 31, 2000 (FEDERAL REGISTER VOLUME 65, NUMBER 211, 64954). IF A COMPANY BELIEVES THAT IT SHOULD BE ABLE TO KEEP ITS PRODUCT ON THE MARKET, IT CAN SEEK A HEARING; THE REQUEST FOR A HEARING MUST BE MADE WITHIN 30 DAYS AFTER THE NOTICE WAS PUBLISHED. TWO COMPANIES ARE CURRENTLY PRODUCING FLUOROQUINOLONE ANTIMICROBIALS FOR THERAPEUTIC USE IN POULTRY (SARAFLOXACIN AND ENROFLOXACIN). ONE COMPANY, WHICH PRODUCES SARAFLOXACIN, HAS REQUESTED A WITHDRAWAL OF ITS APPROVAL AND THEREFORE WILL NOT SEEK A HEARING. THE OTHER COMPANY HAD NOT YET INDICATED IF IT WILL REMOVE ITS PRODUCT FROM THE MARKET. THE FDA DOCUMENT IS AVAILABLE THROUGH FDA'S DOCKETS MANAGEMENT BRANCH, AT HTTP://WWW.FDA.GOV/OHRMS/DOCKETS/98FR/CV0076. PDF. (NOTE: MORE INFORMATION ON FDA AUTHORITY TO REMOVE PRODUCTS FROM THE MARKET CAN BE FOUND AT: HTTP://WWW.FDA.GOV/FDAC/FEATURES/895_RECALLS. HTML).

¶11. CONSISTENT WITH ITS INTERNATIONAL OBLIGATIONS, THE UNITED STATES NOTIFIED FDA'S PROPOSAL TO THE WTO COMMITTEE ON SANITARY AND PHYOSANITARY MEASURES ON NOVEMBER 3. COMMENTS ARE DUE BY JANUARY 2, 2001.

¶12. TALKING POINTS:

-- THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) HAS PROPOSED WITHDRAWING APPROVAL FOR THE USE OF ANTIBIOTICS (ANTIMICROBIALS), SPECIFICALLY FLUOROQUINOLONES, USED THERAPEUTICALLY IN POULTRY. TWO COMPANIES ARE CURRENTLY PRODUCING FLUOROQUINOLONE ANTIMICROBIALS FOR THIS USE. ONE COMPANY HAS AGREED TO WITHDRAW THE PRODUCT VOLUNTARILY FROM THE MARKET, WHILE THE OTHER COMPANY HAS YET TO ANNOUNCE ITS

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INTENTION.

-- THE MAGNITUDE OF THE PUBLIC HEALTH RISK ASSOCIATED WITH ANTIMICROBIAL USE IN ANIMALS HAS BEEN DEBATED FOR OVER THIRTY YEARS.

-- BASED UPON EMERGING SCIENTIFIC EVIDENCE THAT USES, INCLUDING THE THERAPEUTIC USE OF ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS, MAY CAUSE BACTERIA TO DEVELOP RESISTANCE TO THE USE OF THE SAME OR SIMILAR ANTIBIOTICS IN HUMANS, THE FDA ANNOUNCED IN NOVEMBER 1998 DRAFT GUIDANCE FOR INDUSTRY ON THIS SUBJECT. FINALIZED IN DECEMBER 1999, THIS STATED THAT FDA BELIEVES IT IS NECESSARY TO CONSIDER THE POTENTIAL HUMAN HEALTH IMPACT, WHEN APPROVING SUCH DRUGS, OF THE MICROBIAL EFFECTS ASSOCIATED WITH ANTIMICROBIAL "NEW ANIMAL DRUGS" INTENDED FOR USE IN FOOD-PRODUCING ANIMALS.

-- SINCE THE APPROVAL OF FLUOROQUINOLONES FOR THERAPEUTIC USE IN FOOD-PRODUCING ANIMALS IN 1995 AND 1996, SURVEILLANCE DATA HAVE IDENTIFIED A RELATIONSHIP BETWEEN THE APPROVAL OF FLUOROQUINOLONES FOR THERAPEUTIC USE IN POULTRY AND THE DEVELOPMENT OF FLUOROQUINOLONE RESISTANCE

IN CAMPYLOBACTER IN ANIMALS AND HUMANS.

-- FDA'S RISK ASSESSMENT WAS INTENDED TO ESTIMATE THE RISK TO HUMAN HEALTH FROM ANTIBIOTIC RESISTANT FOODBORNE PATHOGENS ASSOCIATED WITH THE DOMESTIC USE OF ANTIMICROBIALS IN FOOD PRODUCING ANIMALS. SPECIFICALLY, A MATHEMATICAL MODEL WAS DERIVED TO RELATE THE PREVALENCE OF FLUOROQUINOLONE RESISTANT CAMPYLOBACTER INFECTIONS IN HUMANS ASSOCIATED WITH THE CONSUMPTION OF CHICKEN TO THE

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PREVALENCE OF FLUOROQUINOLONE RESISTANT CAMPYLOBACTER IN CHICKENS.

-- FDA STATES IN THE NOTICE OF ITS PROPOSAL PUBLISHED OCTOBER 31, 2000 (FEDERAL REGISTER VOLUME 65, NUMBER 211, 64954) THAT IT BELIEVES:

¶1. THE USE OF FLUOROQUINOLONES IN POULTRY CAUSES THE DEVELOPMENT OF FLUOROQUINOLONE- RESISTANT CAMPYLOBACTER, A PATHOGEN TO HUMANS, IN POULTRY;

¶2. THIS FLUOROQUINOLONE-RESISTANT CAMPYLOBACTER IS TRANSFERRED TO HUMANS AND IS A SIGNIFICANT CAUSE OF THE DEVELOPMENT OF FLUOROQUINOLONE-RESISTANT CAMPYLOBACTER INFECTIONS IN HUMANS; AND

¶3. FLUOROQUINOLONE-RESISTANT CAMPYLOBACTER INFECTIONS ARE A HAZARD TO HUMAN HEALTH.

-- FOR MORE SPECIFIC INFORMATION ON THE RISK ASSESSMENT, IT CAN BE FOUND ON FDA'S WEB SITE AT: HTTP://WWW.FDA.GOV/CVM/FDA/MAPPGS/ANTITOC.HTM L

-- THUS, FDA IS PROPOSING TO WITHDRAW THE APPROVAL FOR USE OF ENROFLOXACIN, ONE FLUOROQUINOLONE, IN POULTRY ON THE GROUNDS THAT NEW EVIDENCE SHOWS THE PRODUCT HAS NOT BEEN SHOWN TO BE SAFE.

-- THE COMPANY PRODUCING ANOTHER FLUOROQUINOLONE FOR USE IN POULTRY, SARAFLOXACIN, PLANS TO WITHDRAW THE PRODUCT FROM THE MARKET.

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-- THE UNITED STATES NOTIFIED FDA'S PROPOSAL TO THE WTO COMMITTEE ON SANITARY AND PHYOSANITARY MEASURES ON NOVEMBER 3, AS CALLED FOR UNDER INTERNATIONAL OBLIGATIONS. COMMENTS ARE DUE BY JANUARY 2, 2001.

(IF ASKED)

-- IT IS UNCLEAR AT THIS STAGE IF THIS WILL AFFECT POULTRY PRODUCTS EXPORTED TO THE UNITED STATES. THE FOOD SAFETY AND INSPECTION SERVICE IS EXAMINING THE FDA ACTION TO DETERMINE HOW POULTRY IMPORTS FROM COUNTRIES USING FLUOROQUINOLONES WILL BE HANDLED.
ALBRIGHT

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